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EXAMINER	
KIM, YOUNG J	
ART UNIT	PAPER NUMBER
1637	
MAIL DATE	DELIVERY MODE
12/03/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/692,537	KLUWE, LAN	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,8-10,14 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,8-10,14 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/9/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The present Office Action is responsive to the Amendment received on September 9, 2008.

Preliminary Remark

Claims 1, 4-7, 11-13, and 15-18 are canceled.

Claims 2, 3, 8-10, 14, and 19 are pending and are under prosecution herein.

Claim Objections

Claim 19 is objected to because of the following informalities:

Claim 19 contains a period after each sub-step. MPEP 608.01(m) clearly states that each claim begins with a capital letter and ends with a period and that, "[p]eriods **may not be used** elsewhere in the claims ***except*** for abbreviations."

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The rejection of claim 9 under 35 U.S.C. 112, **second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter, made in the Office Action mailed on March 12, 2008 is withdrawn in view of the Amendment received on September 9, 2008.

The rejection of claims 2, 3, 8-10, 14, and 19 under 35 U.S.C. 112, **first paragraph**, because the specification, while being enabling for a method of determining whether an offspring of an individual afflicted with neurofibomatosis has an increased risk of developing said neurofibromatosis, does not reasonably provide enablement for a method of determining whether an offspring of an individual afflicted with any type of phakomatosis, made in the Office Action mailed on March 12, 2008 is withdrawn in view of the Amendment received on September 9, 2008.

Rejection, Maintained

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 2, 3, 8-10, 14, and 19 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, made in the Office Action mailed on March 12, 2008 is maintained for the reasons already of record.

Applicants' arguments presented in the Amendment received on September 9, 2008 have been fully considered but they are not found persuasive for the reasons set forth in the, "Response to Arguments" section.

The Rejection:

Claim 19 recites the phrase, "determining whether an offspring of an individual afflicted with a phakomatosis, wherein said phakomatosis is a tumor suppressor gene disease *has an increased risk of developing the tumor suppressor gene disease comprising…*" does not make grammatical sense.

Applicants are advised to amend the entire pending claims so that the term, "tumor suppressor gene disease" is replaced with the term, "phakomatosis," so as to maintain consistency in claim terminology and breadth.

Claims 2, 3, 8-10, and 14 are indefinite by way of their dependency on claim 19.

Response to Arguments:

Applicants contend that claim 19 has been amended for clarity (Page 5, 2nd paragraph, Response).

It is respectfully submitted that the amendment does not result in the removal of the above-discussed problem for the following reasons.

Applicants have amended claim 19 to incorporate a comma between the word, "disease" and the word, "has."

This results in the phase which reads, "[a] method for determining whether an offspring of an individual afflicted with a phakomatosis, wherein said phakomatosis is a tumor suppressor gene disease, has an increase risk of developing the tumor suppressor gene disease…"

In other words, is the method drawn to determining whether an offspring of an individual afflicted with a phakomatosis has an increased risk of also developing phakomatosis? Or is the method drawn to determining whether an offspring of an individual with a phakomatosis has an increased risk for developing any tumor suppressor gene disease?

While the phrase, "tumor suppressor gene disease is phakomatosis" may allow one to interpret subsequent iterations of the limitation, "tumor suppressor gene disease" as being limited to phakomatosis, the phrase, "phakomatosis is a tumor suppressor gene disease" does not necessarily limit the later recitations of the limitation, "tumor suppressor gene disease" to phakomatosis"

For the purpose of prosecution, the former interpretation had been and is assumed.

Claim 19 remains indefinite and claims 2, 3, 8-10, and 14 remain indefinite by way of their dependency on claim 19.

Claim Rejections - 35 USC § 103 – Necessitated by IDS

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 3, 8-10, 14, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Allione et al. (International Journal of Cancer, 1998, vol. 75, pages 181-186) in view of Cohen et al. (U.S. Patent No. 5,945,522, issued August 31, 1999) Carbonara et al. (Genes, Chromosomes &

Cancer, 1996, vol. 15, pages 18-25; IDS ref#CA[1] and Skolnick et al. (U.S. Patent No. 5,624,819, issued April 29, 1997).

Allione et al. disclose a method of determining the loss of heterozygosity in a patient suffering from tumor suppressor gene disease (tumor), wherein the method comprises the steps of:

a) amplifying one of more microsatellite polymorphic markers from a patient samples, wherein the samples are both blood and tumor tissue (page 181, 2nd column, *Tumor Samples* and *Genetic-marker analysis*), wherein the mircrosatellite markers are for tumor suppressor gene disease (breast cancer; page 185, 1st column, 1st paragraph; page 185, 2nd column, 2nd paragraph, see the discussion regarding TSG (thus a tumor suppressor genes);

b) comparing the amount and length of the amplified polymorphous DNA microsatellite markers from blood and tumor sample (breast carcinomas; page 185, 1st column, 1st paragraph; see Figure 1);

c) establishing that the loss of an allele in the tumor of the patient based on this comparison (Figure 1).

Allione et al. are not explicit in discussing that the method also further comprise testing of an offspring of the individual, wherein the testing comprises the steps of amplifying for the same microsatellite markers from the blood of the offspring, wherein if the offspring inherits the allele that was retained in the tumor of the patient, determining that the offspring has an increased risk of developing the tumor suppressor gene disease (i.e., breast cancer).

Allione et al. are not explicit in stating that the tumor suppressor gene disease is phakomatosis.

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[1] IDS received on September 9, 2008

Cohen et al. describe a way in which LOH is often employed for deriving at a possible tumor marker:

> "One mapping technique, called the loss of heterozygosity (LOH) technique, is often employed to detect genes in which a loss of function results in a cancer, such as the tumor suppressor genes described above. **Tumor suppressor genes often produces cancer via two hit mechanism** in which a first mutation, such as a point mutation (or a small deletion or insertion) inactivates one allele of the tumor suppressor gene. Often, ***this first mutation is inherited*** from generation to generation." (column 2, lines 57-65).

The artisans continue:

> "As a consequence of the deletion in the tumor suppressor gene, one allele is lost for any genetic marker located close to the tumor suppressor gene. Thus, if the patient is heterozygous for a marker, the tumor tissue loses heterozygosity, becoming homozygous or hemizygous. This loss of heterozygosity generally provides strong evidence for the existence of a tumor suppressor gene in the lost region. By genotyping pairs of blood and tumor samples from affected individuals with a set of highly polymorphic genetic markers, such as microsatellites, covering the whole genome, one can discover candidate locations for tumor suppressor genes." (column 3, lines 4-15).

Carbonara et al. disclose that TSC (Tuberous sclerosis) is implicated by loss of heterozygosity of microsatellite markers linked to 16p13.3 (page 18, 2nd paragraph).

Carbonara et al. discusses:

> "[I]t has been suggested that the 'two-hit' mutation model, already confirmed in more than a dozen tumor suppressor loci... might fit TSC as well. According to this model, a cell should require biallelic loss-of-function mutations at either TSC locus in order to become the progenitor of hamartomas; in a TSC patient, **the first inactivating mutations is likely to be germline**, whereas the second allele is knocked out somatically." (page 21, 2nd column)

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to employ the teachings of Allione et al. and Cohen et al. for method of determining the risk of an offspring of the patient for the same cancer, thereby arriving at the claimed invention for the following reasons.

As already discussed by Cohen et al., it is well known in the art that a cell comprising at least one normal copy of the tumor suppressor gene (i.e., heterozygote) will not give rise to a tumor.

Cohen et al. clearly convey the knowledge of the art, wherein mutation present in parent is inherited in the offspring from generation to generation. Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to assay for the identified microsatellite markers in the offspring, so as to assess the risk of said offspring for the same cancer by determining whether the offspring inherited the same allele which was found to be present in the tumor of the parent patient.

Such concept was clearly present in the art at the time the invention was made as Skolnick et al. demonstrate:

> "One of the hallmarks of several tumor suppressor genes characterized to date is that they are deleted at high frequency in certain tumor types. The deletions often involve loss of a single allele, so-called loss of heterozygosity (LOH), but may also involve homozygous deletion of both alleles. For LOH, the ***remaining allele is presumed to be nonfunctional, either because of pre-existing inherited mutation***, or because of secondary sporadic mutation (column 2, lines 19-24).

Given this knowledge, and with the suggestion made by Carbonara et al. who also point to the same "two-hit" mutations model as Cohen et al. and Skolnick et al.:

> "[I]t has been suggested that the 'two-hit' mutation model, already confirmed in more than a dozen tumor suppressor loci... might fit TSC as well. According to this model, a cell should require biallelic loss-of-function mutations at either TSC locus in order to become the progenitor of hamartomas; in a TSC patient, **the first inactivating mutations is likely to be germline**, whereas the second allele is knocked out somatically." (page 21, 2nd column)

One of ordinary skill in the art at the time the invention was made would have been motivated to employ the teachings of Allione et al., Cohen et al., and Skolnick et al. for the detection of another tumor suppressor gene disease correlated with loss of heterozygosity in TSC genes, that is, phakomatosis, thereby arriving at the invention was claimed. One of ordinary skill in the art

would have had a reasonable expectation of success at arriving at combining the teachings because all of the artisans attribute the tumor suppressor gene disease to the loss of heterozygosity in TSC genes, and that the first inactivating mutations is inherited (i.e., germline mutation).

With regard to claims 3, 5, 8, and 9 the polymorphic microsatellite markers which show LOH in the method of Allione et al. are at least 4 markers in total (Figure 1).

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Double Patenting - Maintained

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The rejection of claims 2, 3, 8-10, 14, and 19 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 6,660,477 (herein, '477 patent), made in the Office Action mailed on April 17, 2007 is maintained for the reasons already of record.

Applicants state a terminal disclaimer will be filed upon indication of allowable subject matter in the application (page 9, bottom to page 10, Response).

As there is no terminal disclaimer filed as of the date of the instant office communication, the rejection is maintained for the reasons of record.

The Rejection:

Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Claims 1-16 of '477 patent are drawn to a method of determining whether an offspring of an individual afflicted with neurofibromatosis, wherein the method comprises the steps of amplifying polymorphic microsatellite markers from tumor and blood samples from the individual afflicted with neurofibromatosis, followed by the amplification of the same polymorphic markers from the offspring from the blood sample, followed by the comparison of the markers from that of the offspring to those of the individual.

Claims 1-16 of the '477 patent are a narrower species drawn to a particular type of condition, while the claims of the instant application is drawn to a genus of tumor suppressor gene disease. Hence, claims of the '477 patent are narrower species of the genus claims of the instant application.

In the instant situation, the narrower species claims necessarily renders the genus claims of the instant application obvious in an "anticipatory" way.

Conclusion

No claims are allowed.

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on September 9, 2008 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 9:00 a.m. to 5:30 p.m (M-F). The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Young J. Kim/
Primary Examiner
Art Unit 1637
12/3/2008

/YJK/